IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appl. No.	:	10/022,014	Confirmation No.: 2793
Applicant	:	Charles K. Brush, et al.	
Filed	:	December 14, 2001	
TC/A.U.	:	1637	
Examiner	:	Cynthia B. Wilder	
Docket No.	:	PU01112	
Customer No.	:	22840	

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P.O. Box 1450
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March 8, 2005

AMENDED APPEAL BRIEF

Sir:

In response to the Notification of Non-Compliance having the mailing date of February 16, 2005, Appellants submit this amended Appeal Brief in triplicate, appealing from the June 29, 2004, rejection of the Primary Examiner, finally rejecting claims 1–14 in the captioned application. The Notice of Appeal was filed on October 4, 2004.

Real Party in Interest

Amersham Biosciences AB, formerly known as Amersham Pharmacia Biotech AB, the assignee and owner of the captioned application, is the real party in interest to this appeal.

Related Appeals and Interferences

There are no other appeals or interferences related to the instant appeal.

Status of Claims

Claims 1-39 are pending in the captioned application. Claims 1-14 are currently under examination, and claims 15-39 have been withdrawn. A copy of the claims currently under examination is appended hereto.

Status of Amendments

There are no outstanding amendments with regard to the captioned application.

Summary of Invention

This invention provides methods for assaying nucleic acid expression utilizing target nucleic acids containing one or more phosphothioate moieties to facilitate more efficient and specific attachment to the probe. The claims are directed to embodiments of the methodology.

Issues

1. Whether claims 1–14 properly rejected under 35 U.S.C. § 103(a) as being unpatentable over Chee, et al. (WO 98/56954) in view of Fidanza, et al. (Journal Am. Chem. Soc. 111, pp 9117-9119 (1989).

Grouping of Claims

All of the rejected claims in the rejection appealed hereunder stand or fall together.

Arguments

1. **Claims 1–14 are not properly rejected under 35 U.S.C. § 103(a) as being unpatentable over Chee, et al. (WO 98/56954) in view of Fidanza, et al. (Journal Am. Chem. Soc. 111, pp 9117-9119 (1989).**

The Examiner has rejected claims 1–14 under 35 U.S.C. § 103(a) as "being unpatentable over Chee et al (WO98/56954 17 December 1998) in view of Fidanza et al (J. Am Chem. Soc. Vol.111 1989 pp. 9117-9119)".

Specifically, the Examiner stated, "Chee et al teach an array with probes which bind to labeled targets both DNA and RNA...," conceding "Chee et al do not teach phosphorothioate conjugation". The Examiner continued, "Fidanza et al teach phosphorothioate conjugation with iodoacetamide...", concluding "one of ordinary skill in the art would have been motivated to apply Fidanza et al's conjugation to Chee et al's detection method in order to increase the facility of attaching reporter groups. Fidanza et al states that the phosphorothioate conjugation provides increased facility in attachment and placement of reporter groups which allowed detailed study in structure and function. Moreover, no cleavage occurs at the sight of attachment. It would have been prima facie obvious to apply Fidanza et al's teaching of phosphorothioate conjugation to various targets...to better study the structure and function of target nucleic acids".

In response, Appellants asserted that the Examiner had not properly combined the teachings of the two references to form a rejection under 35 USC § 103(a). Specifically, Appellants pointed out that WO98/56954 discloses and claims methodology for detecting genetic polymorphisms and monitoring of allelic expressions using a probe array, and acknowledged that the reference does teach that determination of DNA and RNA hybridization profiles, as well as hybridization intensities, can be utilized to characterize specific genotype and/or expression profiles. However, Appellants emphasized that the reference, as the Examiner conceded, does not disclose, nor even suggest, including phosphorothioate conjugation to allow for the attachment of reporter molecules at various stages within the DNA or RNA molecules.

The Appellants further pointed out that the Fidanza, et al. reference discloses a method of covalently attaching reporter groups at specific sites within DNA sequences, which "would simplify detailed study of the structure and dynamics of unusual DNA forms as well as ligand-DNA or protein-DNA complexes" (apage 9117, lines 1-4); continuing this attachment methodology utilizes a chemistry wherein the phosphorothioate diester will covalently bond to an appropriately labeled reporter group. Appellants further pointed out that Figure 1 (pg 9118) discloses a number of labels which can be attached to the DNA molecule, including a PROXYL spin label, a derivative of dihydropyrroloindole subunits, sulfonamide-linked dansyl fluorophores, and N-linked dansyl fluorophores, and the reference notes that these labeled DNA molecules are quite stable and that structural studies of DNA molecules can be determined.

However, Appellants asserted that the Fidanza, et al. reference provides no disclosure, nor even any suggestion, that such methodology would be adaptable, or even

useful, in a probe assay of the type disclosed in the '954 PCT publication. Further, Appellants pointed out that there is no disclosure, nor even any suggestion, the methodology would be useful with RNA expression studies. Indeed, while the Examiner states that the motivation for combining these references would be "to increase facility of attaching reporter groups", the Fidanza, et al. reference and the '954 patent do not, alone or even in combination with one another, remotely suggest that such attachment chemistry would be useful, or even desirable in expression assay methodology.

Appellants further asserted that the Examiner has, at best, shown that it would be obvious to try to utilize the attachment chemistry disclosed in the Fidanza, et al. article in the methodology of the '954 PCT publication, inasmuch as the references themselves provide no such teaching; and asserted that "obvious to try" is not the proper basis upon which a rejection under 35 U.S.C. § 103(a) can be made.

In response, the Examiner stated "Chee et al, states that the array may be used for monitoring the expression level of different polymorphic forms of a gene, particularly different allelic forms of the gene", citing the abstract and page 8. The Examiner continues that the "Chee et al. reference would reasonably read on the term hybridization profile which is a measure of hybridization specific to probe binding". Addressing the lack of motivation argument for the combination of references, the Examiner states, "Fidanza explicitly states that covalent attachment to DNA fragments provides for specific attachment to DNA backbone [sic.] provide for improved study of DNA binding (see page 9117)", concluding "A reasonable expectation of success exist in which Fidanza et al.'s teaching of DNA with phosphorothioate moiety would lead to better emission and detection of the bound target to Chee et al.'s probe array".

In response, Appellants reiterate the argument presented above and respectfully assert that the Examiner is reading something into the cited references which is neither disclosed nor suggested. More specifically, while Appellants concede that the Chee, et al. application does disclose methodology for the measurement of the expression level of polymorphic forms of a gene using a probe assay, Appellants emphasize it does not disclose, nor even suggest, the inclusion of a phosphorothioate moiety in the target nucleic acid. Such phosphorothioate moiety will facilitate the attachment of reporter molecules.

Appellants further respectfully submit that while the Fidanza, et al. reference does disclose a method for attaching reporter groups to a DNA sequence utilizing phosphorothioate diesters, it does not disclose including the same in RNA, which would be the target molecules in the expression assay methodology of Chee, et al. Indeed, contrary to the Examiner's statement, which characterizes the teachings of Fidanza, et al. to include "phosphorothioate conjugations to various targets such as cDNA, RNA and DNA", the entire disclosure of the Fidanza, et al. reference is limited solely to the inclusion of the phosphorothioate in DNA only. The other targets the Examiner states are taught by the reference are, Appellants respectfully assert, neither disclosed nor even suggested.

Thus, Appellants dispute the Examiner's statement that the disclosure of Fidanza, et al. would lead the skilled artisan to have a "reasonable expectation of success" that the disclosure of the Fidanza, et al. reference (phosphorothioate conjugation with DNA) could be combined with the expression (RNA) assay of the Chee, et al. disclosure. Indeed, absent a teaching of the use of the material with RNA, Appellants respectfully

submit all the examiner has shown is that it would be "obvious to try" to combine the two teachings. Such, Appellants respectfully reiterate, is the not the proper foundation for a rejection under 35 U.S.C. § 103(a) to be made.

In view of the foregoing, Applicants respectfully assert the Examiner's rejections cannot be sustained and should be reversed.

Conclusion

In view of the foregoing arguments, Appellants respectfully assert that the Examiner's rejections presented above cannot be sustained, and should be reversed.

Respectfully submitted,

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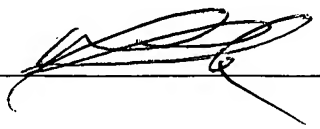
Signature: 

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APPENDIX A

The Rejected Claims

Claim 1 (original): An expression assay, comprising contacting a target nucleic acid with a probe immobilized on a microarray under conditions that allow hybridization between said target nucleic acid and said probe, said target nucleic acid having at least one phosphorothioate moiety.

Claim 2 (original): The method of claim 1, further comprising labeling said target nucleic acid by conjugating a reporter molecule to said phosphorothioate moiety.

Claim 3 (original): The method of claim 2, wherein said labeling step comprises reacting said target nucleic acid with a conjugating moiety that specifically reacts with said phosphorothioate moiety, followed by reaction with a labeling moiety that specifically reacts with said conjugating moiety.

Claim 4 (original): The method of claim 2, wherein said labeling step follows said contacting step.

Claim 5 (original): The method of claim 2, wherein said reporter molecule has an electrophilic moiety.

Claim 6 (original): The method of claim 3, wherein said conjugating moiety is an electrophilic moiety.

Claim 7 (original): The method of claim 5, wherein said electrophilic moiety is selected from the group consisting of a maleimide and an iodoacetamide.

Claim 8 (original): The method of claim 2, wherein said reporter molecule is selected from the group consisting of a fluorophore, a redox moiety, and an electrochemically active agent.

Claim 9 (original): The method of claim 2, wherein said reporter molecule is selected from the group consisting of TMR-maleimide, TMR-iodoacetamide and ALEXAFLUOR-maleimide.

Claim 10 (original): The method of claim 1, wherein at least one nucleotide is a ribonucleotide.

Claim 11 (original): The method of claim 10, wherein said target nucleic acid has at least three different thio ribonucleotides, said thio ribonucleotides being selected from the group consisting of an adenosine thiophosphate, a cytidine thiophosphate, a guanosine thiophosphate, a thymidine thiophosphate, and a uridine thiophosphate.

Claim 12 (original): The method of claim 1, wherein at least one nucleotide is a deoxyribonucleotide.

Claim 13 (original): The method of claim 12, wherein said target nucleic acid has at least three different thio deoxyribonucleotides, said thio deoxyribonucleotides being selected from the group consisting of an adenine deoxyadenosinethiophosphate, a deoxycytidinethiophosphate, a deoxyguanosinethiophosphate, and a thymidinethiophosphate.

Claim 14 (original): The method of claim 1, wherein said target nucleic acid is selected from the group consisting of cRNA and cDNA.

Claim 15 (withdrawn): A method for detecting single nucleotide polymorphism, comprising extending a probe hybridized to a target by exactly one base by incorporating a compound selected from the group consisting of a dideoxynucleoside α-thio triphosphate and an acyclonucleoside α-thio triphosphate.

Claim 16 (withdrawn): The method of claim 15, further comprising labeling the extended probe by conjugating a reporter molecule to the thio moiety of said incorporated compound.

Claim 17 (withdrawn): The method of claim 16, wherein the reporter molecule is selected from the group consisting of TMR-maleimide, TMR-iodoacetamide, Alexafluor-maleimide, and bromo-bimane.

Claim 18 (withdrawn): The method of claim 15, wherein said dideoxynucleoside α-thiotriphosphate is at least one of the group consisting of dideoxyadenosine α-thiotriphosphate, dideoxycytidine α-thiotriphosphate, dideoxyguanosine α-thiotriphosphate, 3'-deoxythymidine α-thiotriphosphate, and dideoxyuridine α-thiotriphosphate.

Claim 19 (withdrawn): A polynucleotide, comprising at least one residue of the group consisting of an adenosine thiophosphate residue, a deoxyadenosine thiophosphate residue, a cytidine thiophosphate residue, a deoxycytidine thiophosphate residue, a guanosine thiophosphate residue, a deoxyguanosine thiophosphate residue, a thymidine thiophosphate residue, and an uridine thiophosphate residue, and at least one moiety bonded to said at least one residue, said moiety selected from the group consisting of a maleimide and an iodoacetamide.

Claim 20 (withdrawn): The polynucleotide of claim 19, wherein said moiety is selected from the group consisting of TMR-maleimide, TMR-iodoacetamide and Alexafluor-maleimide.

Claim 21 (withdrawn): The polynucleotide of claim 19, further comprising a probe hybridized thereto.

Claim 22 (withdrawn): The polynucleotide of claim 19, further comprising a probe hybridized thereto, said probe being attached to a microarray substrate.

Claim 23 (withdrawn): The polynucleotide of claim 19, wherein said polynucleotide is cRNA.

Claim 24 (withdrawn): A molecular probe, wherein said probe terminates in a moiety selected from the group consisting of a thio dideoxynucleotide and an thio acyclonucleotide.

Claim 25 (withdrawn): The probe of claim 24, wherein said probe is a nucleic acid probe.

Claim 26 (withdrawn): The probe of claim 24, wherein said probe is bound to a microarray substrate.

Claim 27 (withdrawn): The probe of claim 26, wherein said probe is a nucleic acid probe and is hybridized to a target nucleic acid.

Claim 28 (withdrawn): A microarray, comprising at least one molecular probe, said probe terminating in a moiety selected from the group consisting of a thio dideoxynucleotide and a thio acyclonucleotide.

Claim 29 (withdrawn): A nucleic acid, said nucleic acid comprising at least three residues of the group consisting of an adenosine thiophosphate residue, a deoxyadenosine thiophosphate residue, a cytidine thiophosphate residue, a deoxycytidine thiophosphate residue, a guanosine thiophosphate residue, a deoxyguanosine thiophosphate residue, a thymidine thiophosphate residue, and a uridine thiophosphate residue.

Claim 30 (withdrawn): The nucleic acid of claim 29, comprising at least four residues of the group consisting of an adenosine thiophosphate residue, a deoxyadenosine thiophosphate residue, a cytidine thiophosphate residue, a deoxycytidine thiophosphate residue, a guanosine thiophosphate residue, a deoxyguanosine thiophosphate residue, a thymidine thiophosphate residue, and a uridine thiophosphate residue.

Claim 31 (withdrawn): The nucleic acid of claim 29, comprising a labeling moiety conjugated to a thiophosphate moiety in at least one of said residues.

Claim 32 (withdrawn): A nucleic acid, comprising cRNA having a thiophosphate nucleotide.

Claim 33 (withdrawn): A cRNA comprising at least one residue selected from the group consisting of an adenosine thiophosphate residue, a cytidine thiophosphate residue, a guanosine thiophosphate residue, and an uridine thiophosphate residue.

Claim 34 (withdrawn): An expression assay kit, comprising a labeling reagent, and a nucleotide reagent, said labeling reagent comprising a thioreactive compound, and said nucleotide reagent comprising a nucleoside α-thiotriphosphate.

Claim 35 (withdrawn): The kit of claim 34, wherein said nucleotide reagent is at least one of the group consisting of adenosine α-thiotriphosphate, cytidine α-thiotriphosphate, guanosine α-thiotriphosphate, and uridine α-thiotriphosphate.

Claim 36 (withdrawn): The kit of claim 34, wherein said thioreactive compound is selected from the group consisting of a maleimide and an alkyl iodide.

Claim 37 (withdrawn): A single nucleotide polymorphism assay kit, comprising a labeling reagent, and a nucleoside triphosphate, said labeling reagent comprising a thioreactive compound, and said nucleoside triphosphate comprising a compound selected from the group consisting of a dideoxynucleoside α-thiotriphosphate and an acyclonucleoside α-thiotriphosphate.

Claim 38 (withdrawn): A method of labeling a nucleic acid that terminates in a residue selected from the group consisting of a dideoxyadenosine thiophosphate residue, a

dideoxyguanosine thiophosphate residue, a dideoxycytidine thiophosphate residue, a 3'-deoxythymine thiophosphate residue, and a dideoxyuridine thiophosphate residue, comprising reacting said nucleic acid with a thioreactive compound.

Claim 39 (withdrawn): A method of labeling a nucleic acid that terminates in a residue selected from the group consisting of an acycloadenosine thiophosphate residue, an acycloguanosine thiophosphate residue, an acyclocytidine thiophosphate residue, a 3'-acyclothymine thiophosphate residue, and an acyclouridine thiophosphate residue, comprising reacting said nucleic acid with a thioreactive compound.